

## REMARKS

Applicant thanks the Examiner for the courtesy of a telephone conference on July 21, 2004 to discuss the pending claims in the instant application. As discussed during that conversation, the pending claims have been amended. Upon entry of the present amendment, claims 35-41 and 50-61 and 65-69 are pending in the instant application. Claims 35, 36, 38, 41, 65 and 67 have been amended, and new claims 68 and 69 have been added.

Support for the claim amendments presented herein is found throughout the specification and in the claims as originally filed. For example, support for the isolated cell clusters recited by amended claim 35 is found at least at page 2, lines 18-19; page 3, lines 12-15; page 4, lines 21-32; page 9, lines 3-5; page 10, lines 1-39; and page 12, lines 19-33. Support for the enriching for liver cell clusters from the canal of Hering, as recited by amended claim 38, is found at least at page 8, line 33-page 9, line 2. Support for the amendment to claim 41 is found at least at page 3, lines 3-11. Support for the methods recited by amended claims 65 and 66 is found at least at page 2, lines 30-32; page 7, lines 1-16; page 8, lines 9-14 and lines 20-22; and in Figures 2-5. Support for the triplet liver cell cluster recited by new claim 68 is found at least at page 2, lines 18-24; page 4, lines 21-23; page 7, lines 17-22; page 10, lines 34-39; at page 12, line 32; at page 14, lines 16-22; and in Figures 5A-5B. Support for new claims 69 is found at least at page 3, lines 1-3; at page 7, lines 1-13; at page 9, lines 13-15; at page 13, lines 6-11 and lines 18-22; and in Figures 4A and 4B. Accordingly, no new matter has been added by these amendments.

### **Claim rejections under 35 U.S.C. §112, second paragraph**

Claims 35-41, 50-61 and 65-67 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite.

#### **Claim 35:**

The Examiner has rejected claim 35 and its dependent claims as being unclear in the recitation of “wherein said population of clusters is enriched for liver stem cells compared to said liver tissue. According to the Examiner, “it is unclear how practicing the method would result in more stem cells than previously present in the liver from which they were obtained.” (Office Action, page 3).

Claim 35 has been amended to recite a method of obtaining a population of liver cell clusters by isolating a liver cell cluster from liver tissue to yield a population of clusters, wherein the cluster consists essentially of a total of 2 to 5 cells at least one of which is a stem cell associated with a hepatocyte, and wherein the stem cell includes an OV6 antigen and lacks an OC2 antigen.

Thus, the pending claims, as amended, do not recite methods of enriching for liver stem cells. Rather, the amended claims are directed to methods of obtaining a population of liver cell clusters. As indicated above, such methods are fully supported by the as-filed specification. Moreover, Applicant submits that the pending claims, as amended, clearly and unambiguously claim such a method for obtaining a population of liver cell clusters. Accordingly, Applicant respectfully requests the withdrawal of this rejection.

Claim 36:

The Examiner has also rejected claim 36 as lacking sufficient antecedent basis for the phrase “the step” or “said step of enriching”. According to the Examiner, claim 36 lacks antecedent basis, because claims 35 and 36 comprise multiple steps and “it is unclear to what step of enriching is [being] referred”. (Office Action, page 3).

Claim 36 has been amended to include the active step of enriching the liver tissue for periportal hepatocytes associated with the biliary tree, wherein the enriching occurs prior to isolating the liver cell cluster from liver tissue. All references to the phrase “the step” have been removed from this claim. In addition, as suggested by the Examiner at page 3 of the Office Action, claim 36 has been amended to indicate that the method recited by this dependent claim encompasses an additional step as compared to the method recited by independent claim 35. As such, Applicant submits that amended claim 36 has sufficient antecedent basis, and this rejection should be withdrawn.

Claim 38:

Claim 38 has also been rejected as being unclear in “the recitation and limitation that the stem cell and hepatocyte are derived from the canal of Hering.” In particular, the Examiner has indicated that it is “unclear if this represents a specific population of clusters or only an indication of where the clusters reside in the liver.” (Office Action, page 4).

As suggested by the Examiner at page 4 of the Office Action, claim 38 has been amended to include the active step of enriching for liver cell clusters from the canal of Hering by identifying and isolating liver cell clusters expressing a bile duct cell marker. As noted above, this method is described throughout the as-filed specification, *e.g.*, at page 8, line 33-page 9, line 2. Thus, Applicant submits that amended claim 38 is clear and distinctly claims a method of enriching for liver cell clusters from the canal of Hering. Applicant, therefore, requests that the Examiner withdraw this rejection.

Claims 65 and 67:

Dependent claims 65 and 67 have also been rejected as being unclear in “the recitation and limitation that the stem cell and hepatocyte are joined by desmosomal junction”. According to the Examiner, it is “unclear if this represents a specific population of clusters, or only a characterization of the cells in the cluster.” (Office Action, page 4).

In accordance with the Examiner’s suggestion on page 4 of the Office Action, claims 65 and 67 have been amended include the active step of isolating a liver cell cluster by identifying a desmosomal junction between at least one stem cell and a hepatocyte. This method is described throughout the specification as originally filed, *e.g.*, at page 2, lines 18-24; page 4, lines 21-23; page 7, lines 17-22; page 10, lines 34-39; at page 12, line 32; at page 14, lines 16-22; and in Figures 5A-5B. Applicant believes that claims 65 and 67, as amended, are clear and definite. As such, this rejection should be withdrawn.

Applicant: Ronald Faris  
U.S.S.N. 09/743,544

### CONCLUSION

On the basis of the foregoing amendments and the Examiner's acknowledgement that the claims are free of the art of record (Office Action, page 9), Applicant respectfully submits that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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Ingrid A. Beattie, Reg. No. 42,306  
Attorney for Applicant  
c/o MINTZ, LEVIN  
One Financial Center  
Boston, MA 02111  
Telephone (617) 542 6000  
Fax (617) 542 2241  
Customer No. 30623

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